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Circadian and Homeostatic Regulation of Human Sleep and Cognitive Performance and Its Modulation by PERIOD3

Derk-Jan Dijk, Ph.D., **Simon N Archer, Ph.D.**

Surrey Sleep Research Centre, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7XP, UK

2. Introduction

We experience the sleep-wake cycle as an alternation between a state of rest, during which consciousness is absent or altered, and a state of active interaction with the social and physical environment, during which the brain engages in many cognitive and other activities. Appropriate timing and adequate quality of the sleep-wake cycle are of paramount importance for successful functioning within our roles at home and at work. According to the conceptual framework of the circadian and homeostatic regulation of the sleep-wake cycle, timing of sleep and waking is achieved through the interaction of two endogenous oscillatory processes and external factors, such as the light-dark cycle and social constraints. Recent progress in the understanding of this interaction of the two endogenous oscillatory processes, the role of clock genes in regulating these oscillatory processes, as well as individual differences in the preferences for the timing of waking activities and sleep, are the topics of this chapter. We will list core and recent references and will also refer to three previous reviews [17;23;24].

3. Circadian and Homeostatic Regulation of Sleep and Cognition

a. Timing of Sleep and Waking Activities: Contribution of Environmental, Social and Internal Biological Factors

Bedtime and wake time are directly observable markers of the sleep-wake cycle, from which both the duration of sleep, as well as its phase relationship with clock time, social and geophysical cycles, can be computed. There is ample evidence demonstrating the impact of social factors on sleep timing. Most of us wake up to meet social requirements such as work schedules, and sleep timing and duration differ markedly between week-days and weekends. Evidence for the important role of light, i.e. the combined contribution of natural and artificial light, in the regulation of sleep and wakefulness comes from multiple sources, including blind individuals who often experience chronic sleep disturbances associated with non-synchronized circadian rhythms [59]. The impact of the geophysical light-dark cycle (as opposed to the light-dark cycle we are exposed to) on the regulation of sleep in our industrialized societies is less profound. Sleep timing with respect to clock time and sleep

Correspondence to: Derk-Jan Dijk, Ph.D., Surrey Sleep Research Centre, Egerton Road, GU2 7XP Guildford UK, +44 1483 824173, d.j.dijk@surrey.ac.uk.

duration are near constant across the seasons, even though in many highly populated areas on our planet the timing of dawn and dusk may change by several hours relative to local clock time, e.g. approximately 4 hours in London, UK. Furthermore, in most people, the sleep-wake cycle remains synchronized with clock time even when we change the phase relationship between clock time and the geo-physical light-dark cycle abruptly, such as occurs during the change to and from daylight savings time. The residual impact of the geophysical light-dark cycle on the timing of the sleep-wake cycle has, however, been observed in analyses of the timing of sleep relative to clock time in people living at similar latitude but different longitudes within one time zone [71]. Evidence for the impact of endogenous biological factors on sleep-wake timing is plentiful. In fact, the magnitude of the effects of endogenous biological factors appears much larger than the impact of external environmental factors and is comparable to the impacts of social factors. This is not to underestimate the profound effect on sleep of local environmental factors, such as traffic noise and ambient temperature. Some characteristics of sleep including its timing and duration differ between men and women [22], and change throughout the life span [66;39], such that older people wake up earlier, while younger people sleep longer. Age-related changes in sleep duration persist when all social constraints are removed [50]. When asked about the preferred timing of sleep and waking activities, including cognitive activities, individuals differ with respect to this diurnal preference. This trait-like characteristic, which differs between men and women and shifts towards morning preference with aging [44], has a heritability of around 50% [53]. The magnitude of the differences in sleep timing across the life span and across the spectrum of diurnal preference, is considerable, i.e., as much as 2–3 hours between young adults and older people [70] and 2–3 hours between larks and owls [34;64]. Despite these differences in timing of the sleep-wake cycle, most healthy people, with the noticeable exception of infants and young children, experience consolidated wake and sleep episodes, during which cognitive performance is upheld throughout the wake episode. We will first describe the endogenous oscillatory processes through which this consolidation of sleep and wakefulness is achieved, before we present the endogenous biological factors contributing to the individual differences in the timing of sleep and wakefulness.

b. Consolidation of Sleep-Wake Cycles Through Opposing Circadian and Homeostatic Sleep Propensity Rhythms

Research during the past 40–50 years has established that the consolidation and timing of the daily sleep-wake cycle is generated by the interaction of two oscillatory processes, the deep or stable circadian pacemaker, located in the suprachiasmatic nuclei (SCN) in the hypothalamus, and the labile oscillator or sleep homeostat, the locus of which is not known and may be diffuse. How the two processes interact has been elucidated through laboratory experiments in which the labile sleep-wake oscillator was scheduled to a periodicity well outside the circadian range [26;86;87]. Because the deep circadian oscillator has a robust endogenous period near to 24-h, living on these non-circadian days leads to sleep and wake episodes occurring at all circadian phases, thereby allowing for an analysis of the contribution of these two oscillators to sleep-wake regulation (See Figure 1) Following initial reports, multiple experiments have now confirmed that the circadian process generates a sleep-wake propensity rhythm that has a phase relationship with the sleep-wake cycle which, although at first sight paradoxical, is highly functional: A circadian wake promoting

signal becomes progressively stronger during the course of the biological day, reaching a maximum shortly before habitual bedtime, at a phase which has become known as the wake maintenance zone, or forbidden zone for sleep. This wake-promoting signal dissipates rapidly after the onset of nocturnal melatonin secretion. Circadian sleep propensity increases as the night progresses to reach a maximum at approximately 7–8 am in healthy young individuals and 6–7 am in older people, which is very close to habitual wake time [30]. The circadian sleep-wake propensity rhythm oscillates in anti-phase with the homeostatic sleep-wake propensity rhythm: Homeostatic sleep propensity is at its minimum at the end of the sleep episode and then increases progressively throughout the waking episode, to reach a maximum just before the habitual sleep episode, which is initiated when the circadian drive for wakefulness subsides. Homeostatic sleep propensity can then dissipate throughout the sleep episode. The hypothesis that consolidation of the sleep-wake cycle is achieved through these opposing homeostatic and circadian sleep-wake propensity rhythms is supported by the observation that after lesions of the SCN, which is the hypothalamic locus of the deep circadian oscillator, the sleep-wake cycle becomes fragmented. Detailed analyses of sleep in intact and SCN-lesioned squirrel monkeys suggest that the SCN primarily generates a strong alerting signal [37]. Other analyses suggest that the SCN also generates a sleep-inducing signal [61]. The importance of the adequate phase relationship between circadian rhythmicity and sleep homeostasis is also underscored by the observation that disruption of the phase relationship between these two oscillators, such as occurs during shift work and jet-lag, leads to disruption of sleep and waking performance.

Not only sleep-wake timing and sleep propensity, but also sleep physiology are profoundly influenced by these two oscillatory processes. This includes basic characteristics of sleep, such as the duration of Rapid Eye Movement Sleep (REMS), the density of rapid eye movements during REM sleep, alpha (8–12 Hz) EEG activity during REM sleep, the incidence, amplitude and frequency of sleep spindles, i.e. 12–14 Hz spindle-like EEG oscillations during nonREM sleep, high frequency EEG activity during nonREM sleep, as well as Slow Wave Activity (SWA; 0.75–4.5 Hz) in nonREM sleep [27;32;49;82]. The latter variable is somewhat unique in that it is primarily determined by the homeostatic oscillator, and only minimally so by the circadian oscillator. In fact, SWA is considered a primary marker of the sleep-homeostat during sleep, also because sleep deprivation will lead to predictable increases in this variable.

The impact of the sleep-homeostat and circadian oscillator on the EEG is not limited to nonREM and REM sleep. The EEG recorded under controlled behavioral conditions during wakefulness is also profoundly influenced by these two oscillators.

For example, alpha activity during wakefulness exhibits a very distinct circadian rhythm with a maximum at approximately 4 pm and a minimum at 6 am, but is also influenced by time awake, such that it diminishes as time awake increases. By contrast, SWA and theta activity (4.5–8 Hz), while also displaying their circadian maxima during the biological day, increase as time awake increases [14]. The latter two variables have been considered markers of the sleep-homeostat during wakefulness, also because sleep deprivation leads to a further increase in these EEG activities. Recent analyses of topographical differences with respect to the circadian and sleep-wake-dependent modulation of EEG activity have suggested that

frontal areas are more affected by the sleep-homeostat than occipital areas, and particularly so for low frequency components of the EEG during sleep [12] and wakefulness[14], as well as EEG spindle activity during sleep [51].

Thus, brain activity, as monitored through polysomnography and the analysis of the EEG during both wakefulness and sleep, is dynamically modulated by the circadian and homeostatic oscillator. The changes in low-frequency EEG activity associated with the duration of wakefulness have been hypothesized to represent use-dependent changes in neural networks [54;78]. Such changes may be more prominent in areas that have been used more intensively, and evidence for local changes in SWA in response to local stimulation has been accumulating [43;47]. Currently, it is thought that wakefulness and the intense sensory stimulation and experience associated with waking behaviors lead to local release of adenosine and growth factors, which in turn may lead to local increases in SWA [8;55].

c. Consolidation of Cognitive Performance Through Circadian Rhythmicity and Sleep Homeostasis

What we experience during wakefulness is our ability to perform. Waking performance includes both physical, e.g. athletic performance, and non-physical performance, e.g. sustained attention. Here we will only discuss aspects of the latter, which we will loosely refer to as cognitive performance (for a discussion on physical performance see [68]). Cognitive performance comprises many different domains and elements including working memory, vigilance, attention, and executive function. A discussion of the brain basis and interrelationships between these domains and elements of cognitive performance is well beyond the scope of this chapter and the expertise of its authors. We merely summarize experiments in which the separate influences of the two oscillatory processes on cognitive performance have been assessed by using multiple performance tasks. Aschoff and Wever already reported that performance is influenced by both the circadian and sleep-wake oscillator [83]. Subsequent experiments have shown that many aspects of performance deteriorate with time awake and improve with sleep. These observations are in accordance with the view that sleep serves to recover from the wear and tear of wakefulness, which interferes with our ability to perform. These experiments have also shown that the circadian influence on cognitive performance is such that performance is poor during the circadian night and better during the circadian day. This basic rhythm of performance has been observed for all performance tests analyzed to date, although minor differences in the timing of peak performance may exist between specific performance tasks [29;44;88]. This suggests that both the circadian oscillator and the sleep-homeostat modulate general determinants of cognitive performance, e.g. arousal, rather than more specific aspects such as executive function only. This view is also consistent with the observation that variables such as core body temperature, which not only display circadian and sleep-wake dependent variation, are correlated with variation in performance on a number of tasks, as first reported by Kleitman and more recently re-investigated and confirmed [84]. It should, however, be emphasized that very few experiments have been designed to investigate specifically how, within a cognitive psychology context, the circadian pacemaker and the sleep-homeostat interact to affect performance. Noticeable exceptions are the experiments conducted by Horowitz [42] and Santhi [72].These latter experiments indicate that the interaction of high sleep pressure and

circadian misalignment leads to decrements in selective attention, and reduced accuracy (fast but sloppy search), as assessed in the visual search task. Harrison and Jones [40] used a sustained attention-to-response task thought to depend heavily on frontal lobe function, to investigate the contribution of time awake and the circadian system to errors related to failure of response (errors of omission) and errors in automatic aspects of responding, related to failure of inhibitory responses, (errors of commission). Interestingly, they reported that both errors of commission and omission were modulated by time awake but not by circadian phase, although the interaction between these two factors was highly significant for errors of commission.

In an analysis of the effects of sleep deprivation and circadian phase misalignment on performance, we found a statistically reliable deterioration on 11 out of 16 performance measures, with no clear differential sensitivity between executive and non-executive tasks [38].

The impact of circadian rhythmicity and sleep homeostasis on aspects of waking function is not limited to performance. The mood of healthy volunteers, as well as patients suffering from SAD, exhibits both sleep-wake-dependent and robust circadian modulation. Mood deteriorates with time awake, recovers during sleep and, from a circadian perspective, is worse in the early morning and best in the evening hours [9;52].

The impact of circadian and sleep-wake-dependent processes on performance extends beyond laboratory conditions. Thus, a contribution of the sleep-homeostat and the circadian oscillator to alertness and mood has been observed in abnormally-entrained and free-running blind individuals while living in their normal environment [58]. These data from the blind also show that the wake-dependent deterioration of mood and performance is not solely dependent on light exposure, but also appears to be associated with wakefulness itself. All of the findings summarized thus far have emphasized the effects of the two oscillatory processes on acute aspects of waking performance. There is a rapidly growing interest in the role of sleep and circadian rhythms in the regulation of longer lasting aspects of performance, i.e. learning, memory and plasticity. Practice effects, i.e. the slow long-term improvements of performance that can be observed in throughput tasks such as the Digit Symbol Substitution and Addition task, are diminished when the phase relationship between the sleep-wake cycle and circadian rhythmicity is disrupted [85]. Whether these differences are related to the sleep disruption or circadian misalignment, cannot be determined from the available data. Implementation of an implicit procedural memory task in experiments designed to elucidate the contribution of circadian rhythms and sleep to waking performance, has revealed that both circadian rhythmicity and sleep pressure modulate the improvement of the learned aspects of this task. Whether this improvement indeed reflects enhanced consolidation or just an improvement in observed performance cannot be deduced from the available data. In a separate line of research, evidence is accumulating that slow wave and sleep spindles are associated with consolidation of procedural and declarative tasks [43;74]. In general, these experiments have emphasized the role of sleep rather than the role of circadian rhythmicity in learning, memory and plasticity, even though many aspects of sleep that are thought to be relevant to its memory consolidating effects, e.g. sleep spindles, are profoundly influenced by sleep homeostasis and circadian rhythmicity [27;32].

The data summarized in this section demonstrate that under conditions of normal entrainment, the phase relationship of the sleep-wake-dependent and circadian changes in performance are such that performance can be maintained throughout the waking episode, because the wake-dependent deterioration is countered by the circadian upswing. When wakefulness is extended into the biological night, performance deteriorates rapidly, because the wake-dependent decline is no longer opposed by the circadian arousal signal. The importance of sleep homeostasis and circadian rhythmicity is not limited to acute performance, but extends to mood as well as the long-term changes in performance associated with learning and memory. Next, we will discuss the nature of the interaction between the two processes, as well as their putative brain bases and neural correlates.

d. Interaction of Sleep Homeostasis and Circadian Rhythmicity: Observed Circadian Amplitude Depends on Homeostatic Sleep Pressure

The notion that the consolidation of sleep and waking performance are regulated by the sleep-homeostat and circadian rhythmicity is widely accepted. The two processes are, in general, thought to be independent: Conceptual and mathematical models have assumed that the two oscillatory processes shape sleep and waking performance in an additive manner [1]. This implies that we can predict sleep propensity and waking performance at any given time by addition of the circadian and homeostatic process. This, in turn, leads to the prediction that the observed amplitude of the circadian modulation is independent of homeostatic sleep pressure, and suggests that the circadian and homeostatic process contribute independently to the variable of interest. There is now a wide range of observations that are at variance with such an additive contribution of the two processes. For example, the amplitude of the circadian rhythm of the propensity to wake up from sleep increases as sleep pressure dissipates. In the initial part of the sleep episode the circadian amplitude is small, i.e. we can sleep at all circadian phases. By contrast, at the end of the sleep episode, when homeostatic sleep pressure is low, the circadian amplitude of the propensity to wake up is very large: We can still maintain sleep consolidation at around the temperature nadir, but sleep becomes very much disrupted on its rising phase. This change in circadian amplitude has been observed for the duration of wakefulness [27] as well as both the frequency and duration of awakenings [28]. The amplitude of the circadian rhythm of the propensity to initiate sleep also changes with sleep pressure [15;16].

One interpretation of this change in observed circadian amplitude is that increased homeostatic sleep pressure inhibits the circadian wake promoting signal and amplifies the circadian sleep promoting signal. Such an interaction between the circadian and homeostatic regulation will lead to more rapid transitions between the vigilance states. The amplitude of the circadian rhythm of EEG characteristics during sleep, such as sleep spindles and the density of Rapid Eye movements during sleep, also changes with homeostatic sleep pressure, such that its amplitude increases as homeostatic sleep pressure dissipates [49]. Evidence for an interaction extends to the EEG during wakefulness, but now the observed amplitude increases as sleep pressure increases. This has been observed for delta and theta EEG activity but not alpha activity, the robust circadian amplitude of the latter variable is not affected by homeostatic sleep pressure [14].

The observed circadian amplitude for several aspects of waking performance also increases with homeostatic sleep pressure, such that the wake-dependent deterioration is minimal during the wake maintenance zone and most pronounced just after the core body temperature minimum [29] and a few hours after the melatonin maximum [88]. This interaction has been observed for several measures on the psychomotor vigilance task, an addition task (See Figure 2), the digit symbol substitution task, the occurrence of slow eye movements and unintentional sleep onset during scheduled wake episodes. These interactions, which were not observed for the probed-recall memory task, were statistically reliable while living on a very long day (42.85 hour forced desynchrony with 28.57 hours of wakefulness) [86]. The observed circadian amplitude of subjective sleepiness, as assessed by the Karolinska Sleepiness Scale, is very sensitive to changes in homeostatic sleep pressure and is already statistically reliable while living on a 20-h day [88].

Additional evidence for an interaction between the two oscillators stems from the observed modulation of the circadian period and amplitude of the melatonin rhythm by the sleep-wake cycle [13]. Thus, even a hormone, the rhythm of which is driven through a multi-synaptic neural pathway from the SCN, is modulated by sleep-wake pressure, although these effects are relatively small [91]. The implication of these observations is that sleep homeostasis and circadian rhythmicity are not independent. The amplitude of any observed circadian rhythm depends on the status of the sleep-homeostat.

The question then arises where in the central nervous system do the circadian and homeostatic oscillator meet and interact. Neuroanatomical and functional evidence suggests that output of the SCN reaches target areas such as the VLPO, TMN LH, thalamus and brain stem nuclei via the DMH [73]. The diffuse activating systems serotonin, orexin, noradrenaline and histamine, which are all under circadian control, impinge on many areas including thalamic and cortical areas. This very much simplified neuroanatomical scheme of circadian modulation of the CNS already implies that the interaction with sleep homeostasis could take place at many different levels. In one scenario, for example, the circadian arousal signals a circadian rhythm of noradrenaline released from brain stem LC neurons [6], or serotonin from dorsal raphe nuclei, which impinge on cortical or thalamic networks to counter wake-dependent changes in these networks. The efficacy of these activating signals may be modified through adenosine, a putative mediator of homeostasis, or depend on the strength of local connectivity. Alternatively, homeostatic sleep pressure may modify the firing patterns of the LC, Dorsal Raphe, or other nuclei of the diffuse activating systems. Other areas in which interaction may occur are the VLPO and neurons synthesizing and releasing orexin. In fact, animal and human studies indicate that orexin is under both circadian and sleep-wake control [89;90] and SCN lesions indeed abolish the circadian rhythm of orexin [20;92].

Finally, evidence for feedback of the sleep-wake cycle and associated changes in SWA onto circadian rhythmicity has emerged at the level of multiple unit activity (MUA) of the SCN. This feedback concerns both acute changes in MUA in response to changes in SWA [21], as well as changes in the circadian amplitude of MUA in response to partial sleep deprivation [19]. These observations show that the interaction of sleep homeostasis and circadian rhythmicity extends to an output that is very close to the core circadian oscillator. Whether

sleep homeostasis indeed can modulate the amplitude of circadian rhythms at the level of clock gene expression and translation, which are thought to constitute the core of the circadian oscillations in humans, remains unknown, although animal studies have provided evidence for such interactions [60]. Thus, there is now abundant evidence for an interaction of circadian rhythmicity at many different levels of description and many different areas in the brain. The discovery, that canonical clock genes are not only expressed in the loci of the circadian pacemaker but also in many other brain areas, adds another level of complexity with respect to the possible ways in which circadian rhythmicity and sleep homeostasis may interact.

Whatever the exact nature of locus of the interaction may be, one implication of the interaction is that differences in observed circadian amplitude may be related to differences in homeostatic sleep pressure.

4. Interindividual Differences in Circadian-Sleep Phenomenology and the Role of Clock Genes

Individuals differ with respect to the timing and duration of sleep, their preferred timing for waking activities including cognitive tasks, and their ability to maintain wakefulness and cognitive performance during sleep loss and circadian misalignment. Many of these characteristics have been shown to be trait-like and variations in circadian and sleep physiology and genetic makeup associated with these phenotypes are being investigated intensively.

a. Circadian correlates - physiology and clock gene expression

One line of investigation into circadian and sleep phenotypes is inspired by classical circadian entrainment theory, according to which the phase of a circadian pacemaker is determined by its intrinsic period (as well as light sensitivity and light exposure, which we will not discuss in this chapter). Variation in sleep-wake timing is predicted to be associated with variation in the phase of physiological markers of the circadian pacemaker, even when assessed in the absence of the sleep-wake cycle, i.e. constant routine conditions. These differences in phase are, in turn, predicted to be associated with differences in endogenous circadian period. The timing of the melatonin and core body temperature rhythms are earlier in morning types than evening types [35], and the endogenous period of these variables, as assessed during forced desynchrony, is shorter in the former group [33]. The association between entrained phase and endogenous period is reliable in young individuals but not in older people. Associations between sleep-wake timing and circadian markers extend to the level of clock gene expression *in vivo* and *in vitro*. Many clock genes are rhythmically expressed in peripheral tissues and cells including peripheral blood cells in humans [5;10;56] (See Figure 3). In young adults, the timing of the rhythm of RNA expression of *PER3* in leukocytes, as assessed under constant routine conditions, is associated with habitual sleep-wake timing, although this association is much weaker than the association with the melatonin rhythm [5]. This association was not significant for the clock genes *PER2* and *BMAL1*. The period of circadian gene expression, as monitored *in vitro* in fibroblast cell cultures through a luciferase reporter gene driven by the *Bmal1* promoter, differs between

morning and evening types [11]. Morning types had an average period of 24.33 compared to 24.74 in evening types and entrained phase correlated with period length, although there was significant spread and overlap between the two sets of data. This implies that other factors could account for circadian behavioral variation. Differences in the amplitude of clock gene expression could affect phase of entrainment and the study showed that in individuals with normal circadian period, the morning subjects had low clock gene expression amplitude compared to high amplitude in the evening types, which also correlated with larger phase shifts in the morning types.

The circadian oscillator has also been implicated in inter-individual differences in sleep duration. Short sleepers, have a shorter biological night, as indexed by the period of melatonin secretion, than long sleepers [3].

b. Homeostatic correlates

In another line of investigations, differences in sleep-wake timing and preference for the timing of waking activities are related to differences in the sleep-homeostat. It has long been known that morning types have more SWS and SWA, in particular in the beginning of the sleep episode, and a more rapid decline of SWA during sleep [48;57]. This was recently confirmed in a series of analyses in which morning and evening types were subdivided into those who had an early or late circadian phase, and those who had a normal circadian phase, despite an extreme diurnal preference [62–64]. These analyses have suggested that people may be morning types either because of an early circadian phase, or a more rapid build-up of homeostatic sleep pressure and associated changes in neural networks. In fact, it has been reported that during wakefulness, theta activity in the EEG increases more rapidly in morning types than evening types [76]. Individual differences in SWS and SWA, primary markers of the sleep-homeostat, have been linked to polymorphisms in the Adenosine-2 receptor and adenosine deaminase [69], but whether these changes have functional consequences for waking performance remains to be established.

c. Amplitude correlates

Analyses of the association between diurnal preference, as assessed by the Horne-Östberg questionnaire [41], with patterns of clock gene expression *in vitro* have shown that part of the diurnal preference variation can be explained by differences in circadian period, but an approximately equal portion of the variance can be explained by differences in amplitude of clock gene expression [11]. Young and older people differ with respect to their ability to perform when wakefulness is extended into the biological night. Whereas young people show a very strong deterioration of performance during the circadian night, the apparent circadian amplitude of this performance decrement is very much attenuated in older people [2]. However, it should be noted that SWS and SWA are also very much reduced in older people. Because the observed circadian amplitude is a consequence of the interaction of homeostatic sleep pressure and circadian rhythmicity [27;29], it may very well be that differences in homeostasis underlie these age-related changes in circadian amplitude of performance deterioration.

d. Role of *PER3* in the circadian and homeostatic regulation of sleep and cognition

The clock gene *Per3* is thought to exert a statistically significant but minor impact on traditional circadian assays such as free-running period in animals [7;75]. In humans, the role of this clock gene has been investigated by analyzing the association of polymorphisms in the gene with circadian and sleep phenotypes. To date polymorphisms in *PER3* have been reported by a number of laboratories to be associated with diurnal preference and delayed sleep phase syndrome [4;36;67]. We have reported that a primate-specific [81], variable number tandem repeat (VNTR) polymorphism in *PER3*, the allele frequency of which varies with ethnicity [65], exhibits a statistically significant but weak association with diurnal preference, as assessed with the Horne-Örtberg scales. Individuals homozygous for the longer, 5 repeat allele ($PER3^{5/5}$) are more likely to show morning preference than individual homozygous for the shorter, 4 repeat allele ($PER3^{4/4}$) [4] and the strength of this association declines with age [46]. As we have seen above, diurnal preference is a complex phenotype and may be determined by differences in both circadian rhythmicity and sleep homeostasis, among other unidentified factors. To investigate the contribution of the VNTR *PER3* polymorphism to circadian and sleep physiology, we conducted a prospective study in which individuals were selected only on the basis of their *PER3* VNTR genotype. We next characterized sleep physiology, circadian physiology, and the effects of sleep loss and circadian misalignment on cognitive decline in subjects homozygous for the longer or shorter allele. No differences between the genotypes with respect to circadian physiological markers, such as the phase and amplitude of the melatonin and cortisol rhythm in plasma, or the phase and amplitude of clock gene expression in leukocytes, were observed. However, traditional markers of sleep homeostasis, i.e. SWA during sleep and the increase of theta activity during wakefulness and during sleep deprivation, as well as the autonomic control of heart rate during sleep [80] indicated a more rapid increase of homeostatic sleep pressure in $PER3^{5/5}$[79]. This more rapid increase in homeostatic sleep pressure was associated with a more rapid decline in a composite measure of cognitive performance during the biological night, i.e. the apparent amplitude of the cognitive performance rhythm was much greater in $PER3^{5/5}$ than in $PER3^{4/4}$. (See Figure 4) Detailed analyses of the performance data showed that even though sleep loss and circadian phase misalignment affected many performance measures, the effects of genotype on deterioration of performance in the morning was particularly pronounced for measures of executive function, such as the verbal and spatial n-backs, paced visual serial addition tasks, and the delay in response on a serial addition task when a predictable sequence is replaced by a random sequence [38]. This observation, when replicated, may suggest that clock genes could affect specific aspects of cognition, even though these specific aspects may also be mediated through effects on sleep homeostasis.

e. Modeling the effects of *PER3* on sleep homeostasis, circadian rhythmicity and the cognitive decline during sleep loss.

We developed a simple conceptual model to describe the effects of the VNTR polymorphism. In this model, it is assumed that the VNTR exerts its effect through effects on sleep homeostasis. The nature and mechanism of these effects are unknown, but could be related to effects on neural metabolisms that lead to more rapid changes in local connectivity in response to wakefulness in $PER3^{5/5}$, or alternatively reflect differences in activating influences on the EEG, which may appear as changes in sleep homeostasis. The time course

and absolute values of SWA during baseline and recovery sleep are consistent with a more rapid buildup and decline of H in *PER3*$^{5/5}$ individuals [79], and this is reflected in the differential time course of process S (See Figure 5). Thus, during a normal sleep-wake cycle, the amplitude of the H oscillator is greater in *PER3*$^{5/5}$ than in *PER3*$^{4/4}$. The physiological and molecular circadian data are consistent with an identical amplitude and phase of a core circadian oscillator C, and we have, therefore, assumed Process C to be identical. Based on data from forced desynchrony protocols, we assume that this process C generates a wake-promoting signal and a sleep-promoting signal. The feedback of sleep homeostasis on the process implies that the amplitude of the wake and sleep promoting signals is modulated by H, such that the wake-promoting signal is inhibited by H and the sleep-promoting signal is amplified by H. As a consequence the amplitude of the C process modulated by H is greater in *PER3*$^{5/5}$ than in *PER*$^{4/4}$. Performance is represented by the difference of this C*H process and H. Under these assumptions performance is near stable throughout a waking day in both *PER3*$^{5/5}$ and *PER3*$^{4/4}$, although minor differences between the two genotypes do emerge. Whereas in *PER3*$^{5/5}$ performance reaches its maximum just after awakening in the morning, in *PER3*$^{4/4}$ this maximum is reached in the evening hours, just prior to bed-time. When wakefulness is extended into the biological night, the differences between the two genotypes escalate. This is not because the difference in H becomes much greater between the two genotypes, but because of the interaction of H and C. The essence of the model is that a difference in the kinetics of a homeostatic process leads to differences in the negative effects of sleep loss in performance, in particular during the circadian morning. Thus, what is an apparent circadian phenotype derives from differences in sleep homeostasis.

A mutation in *PER2* has been reported to affect the timing of sleep in members of a family afflicted with FASPS [77]. To date, only effects on traditional circadian markers, i.e. phase and period [45], have been reported for this mutation and the available sleep physiology data are insufficient to warrant any conclusion with respect to effects on sleep homeostasis. However, animal experiments have shown that disruption to the clock genes *Cry1*, *Cry2*, *Clock*, *Npas2*, *Bmal1* and *Dbp* all lead to effects on sleep physiology or EEG derived parameters of sleep homeostasis (reviewed in [31]).

5. Conclusion

Maintenance of performance throughout consecutive waking episodes requires adequate alignment of a circadian arousal rhythm with the sleep-wake homeostat. The two systems interact dynamically and contribute to many aspects of sleep physiology and waking performance, including learning and memory. How aspects of sleep physiology and their circadian and homeostatic regulation relate to performance, remains largely unknown, although a role for slow-wave sleep is often implied. The close interaction between circadian rhythmicity and sleep homeostasis is underscored by the interdependence of circadian amplitude and homeostatic sleep pressure for many sleep and performance measures. Such a close interdependence is also consistent with the effects of clock genes on sleep homeostasis and the effects of the VNTR polymorphism in *PER3* on markers of sleep homeostasis and cognitive decline in the early morning following sleep loss. Understanding the effects of these alterations in clock genes at the cellular level may provide insights into the nature of the sleep-homeostat and its interaction with circadian rhythmicity.

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1. Synopsis

Sleep physiology and waking performance are regulated through the interaction of an endogenous circadian process and a sleep-wake-dependent homeostatic process. The two processes are not independent: the observed circadian amplitude of waking performance depends on homeostatic sleep pressure, such that the negative effects of sleep loss are most pronounced in the early morning if homeostatic sleep pressure is high. Genes that are associated with circadian and/or sleep phenotypes in humans have been identified. The variable number tandem repeat polymorphism in *PERIOD3,* which is associated with morningness-eveningness, predicts inter-individual differences in cognitive decline in the early morning after sleep loss. This phenotype can be understood through the polymorphism's effects on sleep homeostasis, which in turn leads to an apparent increase in the circadian amplitude of cognitive performance. These findings underscore the close interrelations between sleep, circadian rhythmicity and waking performance, and imply that some circadian phenotypes are related to changes in sleep regulatory processes. Understanding the effects of clock genes at the cellular and biochemical level may provide insights into the nature of the sleep-homeostat and its interaction with circadian rhythmicity in the regulation of waking performance.

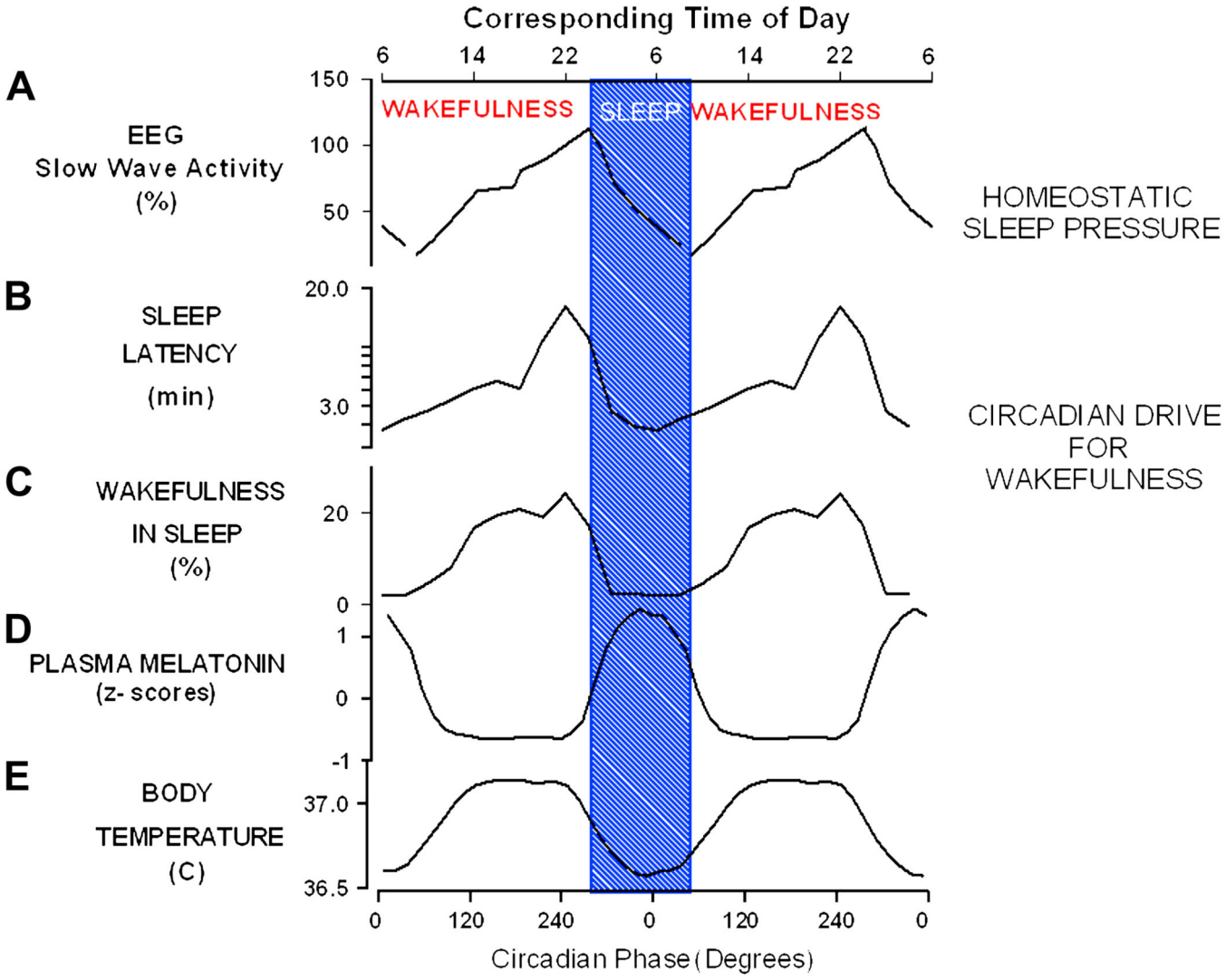

Fig 1.

Circadian and homeostatic regulation of sleep and wakefulness in humans. Panel A: Increase of homeostatic sleep pressure during wakefulness and its dissipation during sleep as reflected in EEG SWA during daytime naps and nocturnal sleep [25]. Circadian variation in wake/sleep propensity as reflected in the latency to sleep onset (Panel B) after 18h:40 min of wakefulness and wakefulness (Panel C) in sleep opportunities, measured during forced desynchrony of the sleep-wake cycle and endogenous circadian rhythms of melatonin (Panel D) and core body temperature (Panel E) [30]

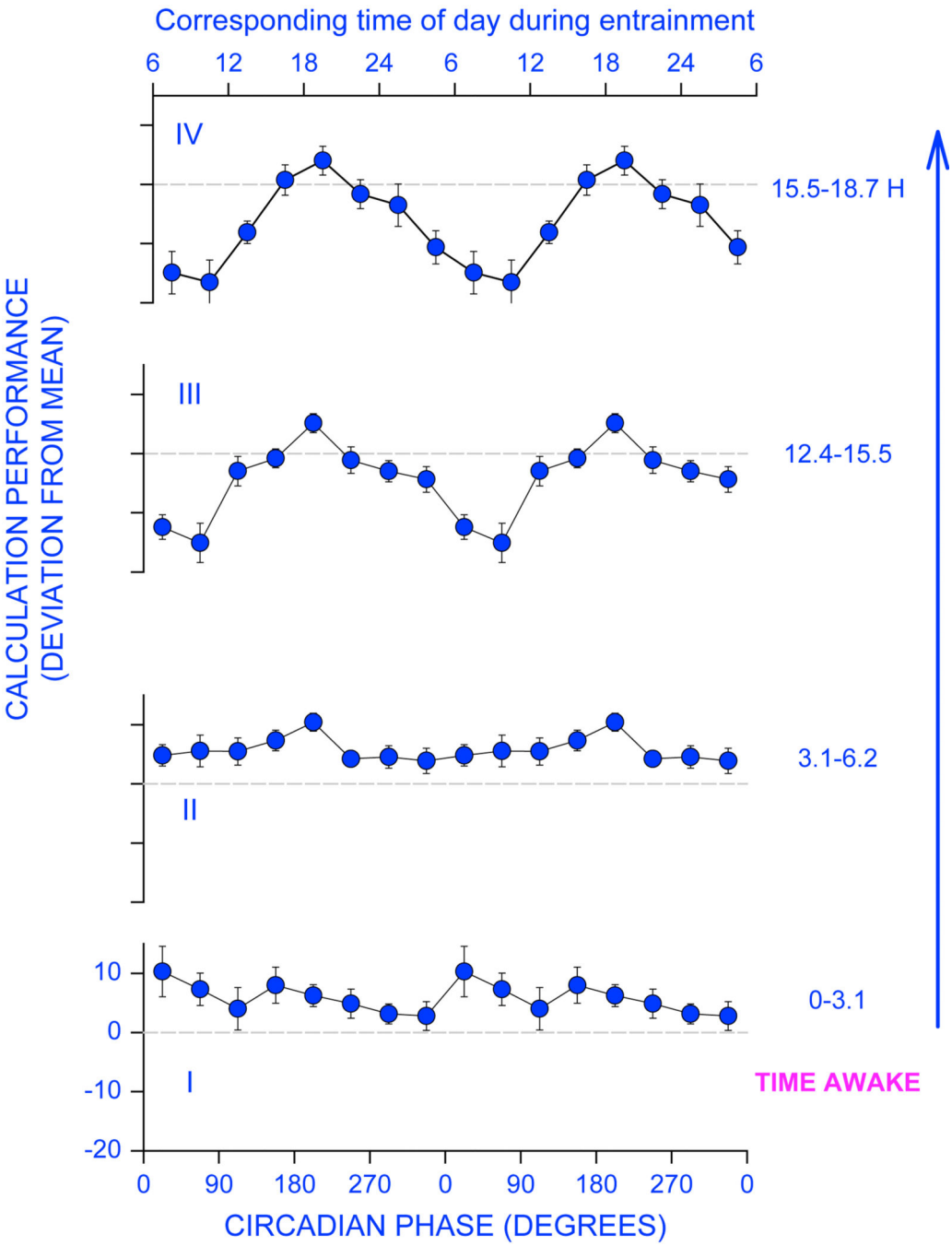

Fig 2.

Increase in the apparent circadian amplitude of calculation performance with increasing homeostatic sleep pressure. The circadian variation in performance was assessed while subjects were schedule to 28-h sleep-wake cycles in a forced desynchrony protocol, and data were segmented per quarter of the 18h:40 min scheduled wake episode. Whereas during the first quarter (0–3.1 hours awake), the circadian amplitude is very low, it increases progressively such that during the last quarter performance is very much impaired, in

particular at and shortly after the nadir of the core body temperature rhythm (o degrees). Modified from [18;29].

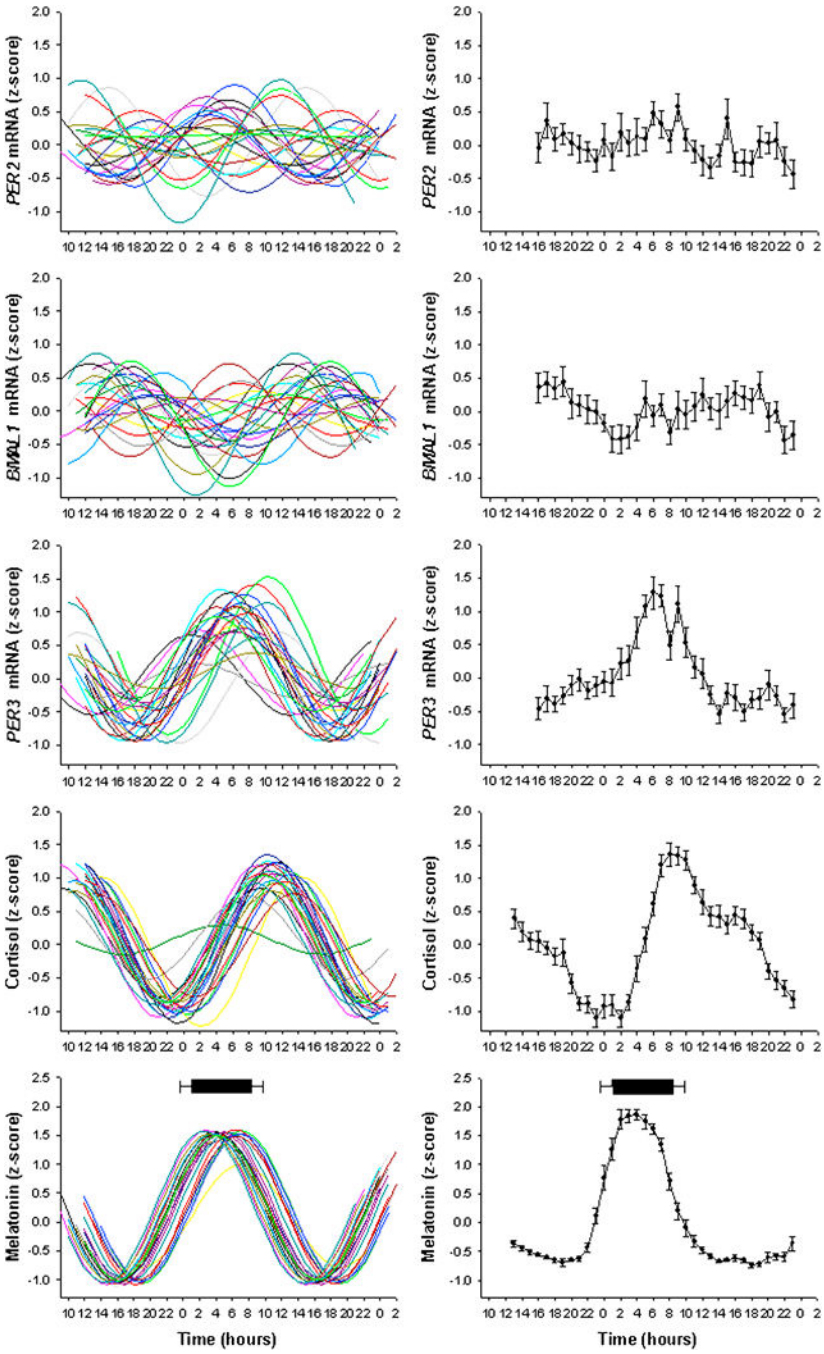

Fig 3.

Individual and average oscillations in endocrine and mRNA markers of circadian rhythms assessed during constant routine conditions. Left Panel: z-scored normalized rhythms for *PER2*, *BMAL1*, *PER3*, melatonin and cortisol plotted relative to clock time. Right Panel: Average z-score curves (±SD). Mean sleep onset and wake times (±SD) are indicated by the black bar above the melatonin profile. With permission from [5].

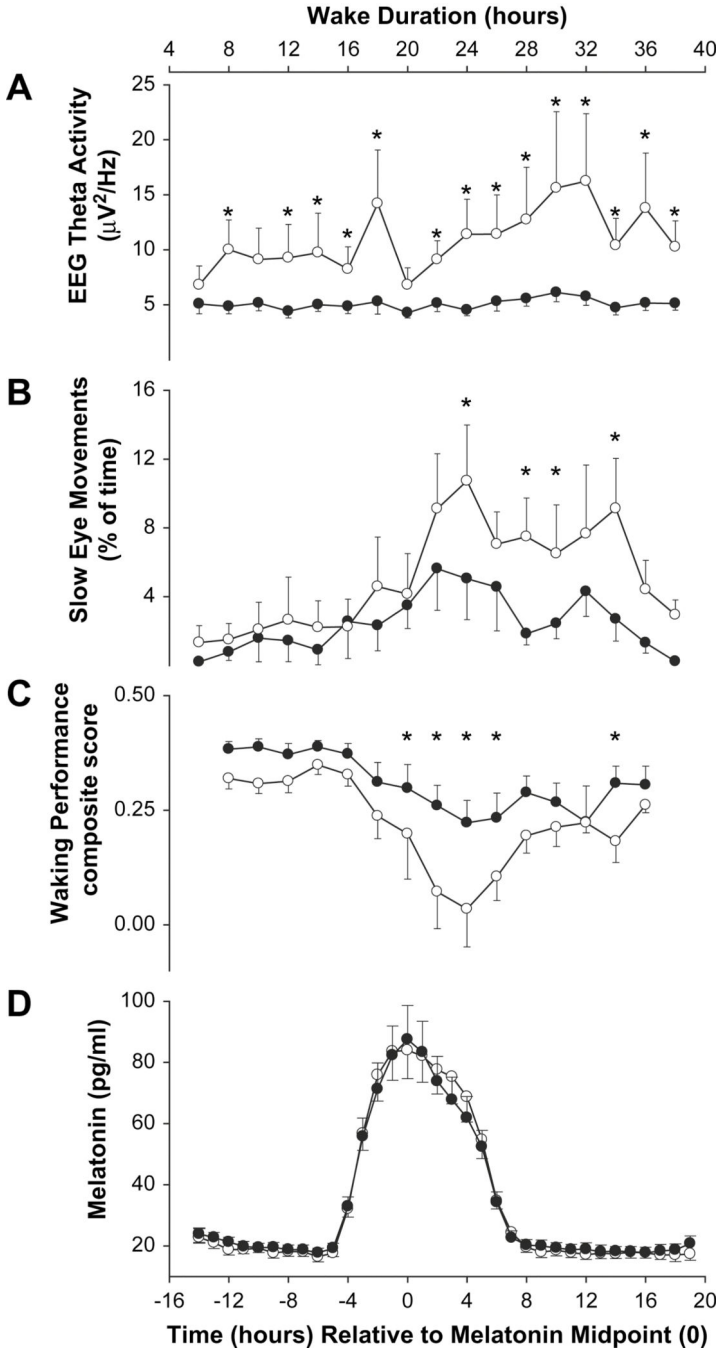

Fig 4.

Faster increase of homeostatic sleep pressure and more rapid deterioration of waking performance in *PER3*$^{5/5}$ (open symbols) than *PER3*$^{4/4}$ (filled symbols) during approximately 40 h of wakefulness. Homeostatic sleep pressure is assessed by increase of theta EEG activity and slow eye movements during wakefulness. Error bars represent SEMs. Data are plotted relative to the melatonin midpoint. With permission from [79].

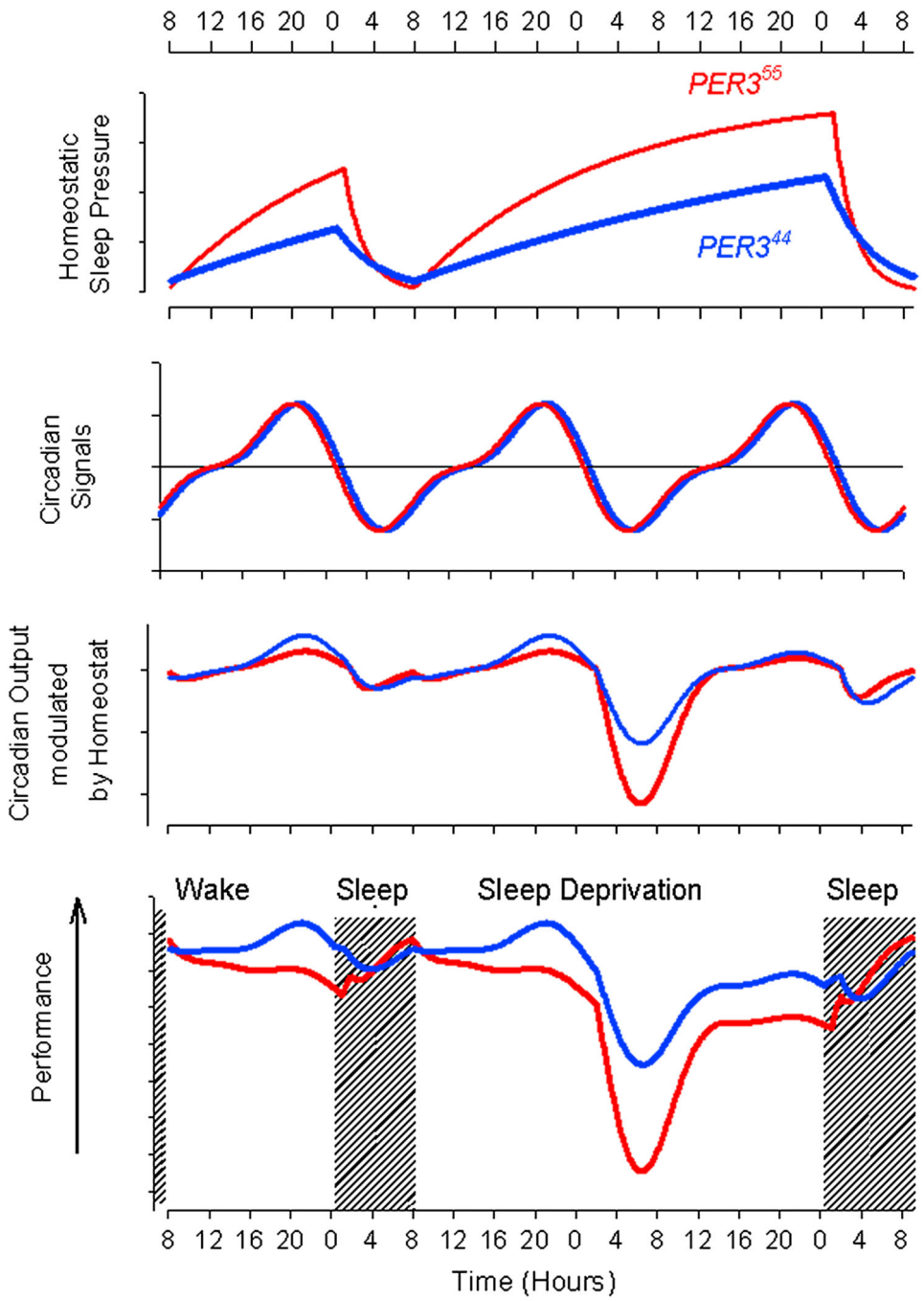

Fig 5.

Conceptual model for the regulation of sleep-wake and performance in *PER3*$^{5/5}$ and *PER3*$^{4/4}$. Top panel: A circadian signal promoting wakefulness (black) and sleep (red) does not differ in either phase or amplitude, between the genotypes. Second Panel: The homeostatic process S, increases during wakefulness and declines during S. The time constants of this process are shorter in *PER3*$^{5/5}$ than in *PER3*$^{4/4}$ and there the amplitude of the S oscillation during a normal sleep-wake cycle (left side of panel) is greater in *PER3*$^{5/5}$.

During sleep deprivation (right side of panel) there is a prolonged increase in Process S followed by its return to baseline during recovery sleep.

Third Panel. The circadian process modulated by S. Please note that at the end of the waking day, the attenuation of the wake promoting signal by homeostatic sleep pressure is greater in *PER3*$^{5/5}$ than in *PER3*$^{4/4}$, during sleep deprivation, the sleep-promoting signal, which is maximal in the morning hours, is amplified by homeostatic sleep pressure and more so in *PER3*$^{5/5}$ than in *PER3*$^{4/4}$. Performance, which is a simple function of (C modulated by S) and S, is near stable during a normal waking day, although a small decline is observed in *PER3*$^{5/5}$ (typical for morning types) and in *PER3*$^{4/4}$ (typical for evening types) performance increases. During sleep deprivation performance is poorest in the early morning hours and in particular so in *PER3*$^{5/5}$. Please note the correspondence between this time course and the time course of performance in Fig 4.